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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/776,350	04/18/1997	ALASDAIR R. MACLEAN	117-231	1818

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/776,350	MACLEAN ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *43-45,47,51 and 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *43-45,47,51 and 59-61* is/are rejected.

7)☐ Claim(s) *61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Declaration and Amendment filed October 12, 2004 in response to the Office Action of May 10, 2004 is acknowledged and has been entered. Previously pending claims 46, 48-50, 52-58 have been canceled, claims 43, 47, 59 have been amended and new claims 60-61 have been added. Claims 43-45, 47,51, 59-61 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC 103

4. Claims 43-45, 47, 51, 59 remain rejected and claims 60-61 are rejected under 35 USC 103 for the reasons previously set forth in the paper mailed May 10, 2004, Section 3, pages 2-8.

It is noted that the Brown Declaration specifically teaches that HSV replication cycles can be either lytic or non-lytic (p. 4 of the Declaration) and it is possible for viruses to replicate yet not be considered virulent because the replication cycle has been blocked at a stage before the virus is able to cause cell death and disease (p. 4 of the Declaration), *in vitro* lysis cannot be equated with the ability of that virus to replicate in the same cells *in vivo* since *in vitro* cells can be manipulated to enable lytic replication (p. 5) wherein 80% of the world's population have a latent HSV infection and if it were virulent, then there would be death of the individual and 80% of the population would not survive (p. 5 of the Declaration). The Declaration concludes that replication of a virus is not necessarily lytic or virulent (p. 5 of the Declaration).

Applicant states that replication of HSV *in vivo* can take place by one of two modes, either lytic replication or latent replication (p. 6 of Response), reiterates

Examiner's statement that HSV1716 is "capable of killing non-neuronal tumor cells via oncolysis since it retains the ability to replicate in peripheral tissues" and argues that Examiner is incorrect because replication is not equivalent to virulence or lysis and states that *in vivo* lytic replication is not necessarily occurring and specifically states that for a given HSV, its behavior *in vitro* is not a direct indicator of its behavior *in vivo*.

The argument has been considered but has not been found persuasive because although replication is not equivalent to virulence or lysis and *in vitro* lysis can certainly be experimentally manipulated, as Applicant clearly states, it is well known in the art that replication of HSV *in vivo* can take place by one of two modes, either lytic replication or latent replication. Therefore it would be expected that at least a subset of the infected tumor cells of the combined references would in fact be lysed, given that the replication of HSV *in vivo* can take place by either of the two modes identified by Applicant and in particular because US Patent No. 6,139,834 specifically teaches that the HSV vector of the invention is capable of killing human tumor cells *in vivo* as previously set forth. Clearly, this is not latent replication. Although the reference does not specifically teach that the HSV of the invention lyses the tumor cells, the invention of the combined references, that is the method with the HSV construct appears to be the same as the prior art methods, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method and product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences.

See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Applicant argues that Examiner's statements on pages 4 and 6 are inconsistent wherein Examiner says that the genetically altered viruses sought in Martuza are not capable of replication in non-dividing cells to avoid systemic infection which highlights the suggestion in Martuza that viruses that are non-replication competent in non-dividing cells are required, but then combines that teaching with the ability of 1716 to replicate in peripheral, and in most cases non-dividing tissues.

The argument has been considered but has not been found persuasive because contrary to Applicant's argument, Examiner is not inconsistent since Examiner specifically points to the non-neurovirulence of 1716 and the rejection is drawn specifically to the treatment of tumor cells within the nervous system and the requirement for non-neurovirulence that is a replication defect in the central nervous neuron environment. Clearly the 1716 HSV are non-replication competent in non-dividing cells of the CNS, the site of treatment of the method of the combined references.

Applicant reiterates that replication is not equivalent to and does not always lead to lysis and argues that such information about replication of a given HSV in certain tissues does not in itself indicate whether or not one can expect that virus to be virulent for that cell type. The argument has been considered but has not been found persuasive for the reasons set forth previously and above.

The Brown Declaration teaches that metastasized tumor cells retain the lineage of the parent tumor, regardless of site of metastasis. The behavior of a secondary tumor in an unrelated organ is different from the behavior in the organ

of origin in that the biochemical environment is different and thus it does not follow that a treatment which is effective for a primary tumor will necessarily be effective for a secondary tumor (p. 2 of the Declaration) and anti-cancer treatments targeted at, for example, hormonal control would not be expected to be effective in an organ wherein the hormone is not present (p. 3 of the Declaration).

Applicant argues that primary and secondary tumors represent distinct neoplastic tissue and can be distinguished by different biochemistry, morphology, genetic markers and responsiveness to treatment and it is not uncommon to find that the primary tumor is treated with some degree of success only to find that a secondary tumor, derived from the primary tumor is unresponsive to the treatment successfully employed for the primary tumor.

The arguments have been considered but has not been found persuasive because contrary to Applicant's arguments, secondary tumors do not represent distinct neoplastic tissues, but rather, as Dr. Brown has pointed out, they retain the lineage of the parent tumor, regardless of the site of secondary tumor. Further, only in answer to Applicant's argument, although differences between metastatic and primary tumors are known in the art, these differences are generally directed to changes that support the invasion process and that support the continued replication and survival of the cancer cells such as the impairment of tumor suppressors or the overexpression of oncolytic factors as exemplified by the art recognized mutation of the p53 tumor suppressor, a mutation found in nearly 50% of all tumors and as clearly disclosed in Zudaire et al, (Regulatory Peptides, 2003, 12:175-183) who specifically teach that malignant growth is dependent upon a multistep process including basic essential alterations such as evasion from apoptosis, self-sufficiency in growth signals, angiogenesis and metastasis (p. 175,

col 2). It is certainly unclear, given the teaching, why alterations in HIV-1 infectivity would be productive in the multistep processes involved in malignancy. In addition, although the infection of tumor cells with HSV-1 vectors was well known in the art at the time the invention was made, an in-depth search of the 74 databases of the STN bioscience group has not revealed a single instance of any cancer cell mutated in a way to prevent HSV-1 infection. Further, even if such a mutation had occurred, it would not be expected that all of the metastatic cancer cells would contain such a mutation and it would be expected that at least a subset of the metastatic cancer cells would infectable. As Dr. Brown clearly points out on page 4, infection of cells with HSV can occur by a variety of mechanisms including cell fusion of infected and uninfected cells and by the formation of syncitia, thus even if only a subset of the cancer cells were infectable through cell surface mechanisms, given the multiple infection pathways as disclosed by Dr. Brown, it would be expected that the method of the combined references would be successful for the reasons of record.

Applicant argues each of the references separately on pages 8-16. It is noted that Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981).

As drawn to US Patent No. 6,139,834, Applicant argues that the construct of the invention is drawn to a combination of mutations, rather than a single mutation and therefore the '834 patent is not a proper reference. The argument has been considered but has not been found persuasive because the claims as currently constituted do not limit the number of mutations for the reasons of record. It is noted that amendment of claim 43 to delete the term "such" and substitute therefore the term "said", deletion of the term "a" after "the wild-type by", deletion of the term "a" after "modification consists of" would obviate the instant rejection.

Applicant further argues that Martuza only describes killing of primary tumor cells and although claim 3 and column 3 list many tumor types, all of those listed relate only to primary tumor cells and the description and context of the patent does not indicate otherwise. The argument has been considered but has not been found persuasive because a review of the '834 patent reveals that the only primary cancer cells referred to are glioma cancer cells. Although the specification clearly teaches that human tumors including melanoma are amenable to the claimed treatment, there is no limitation either in the claims or the specification that the cells to be treated are primary cancer cells. In addition, although the specification teaches that primary tumor cells can be cultured, the specification exemplifies the infection of a human melanoma cell line which is clearly not a primary tumor.

As drawn to WO 92/13943, Applicant reiterates arguments drawn to the ability to replicate is not equivalent to virulence. The argument was considered above and is not convincing for the reasons set forth above.

As drawn to Bolovan, Applicant extensively argues that the mutants created by Bolovan were not completely avirulent as far as CNS tissues are concerned and

argues that the Applicant further points to the importance of the physiological state of the cell in overcoming the restriction of replication of 34.5 mutants wherein the experiments are performed *in vitro*. Applicant further argues that a metastatic tumor in the CNS is distinct from a culture of mouse embryo cells. The argument has been considered but has not been found persuasive as Applicant is certainly arguing the reference individually. In particular, the reference was cited only to demonstrate that 34.5 mutated HSV-1 replicate efficiently *in vitro* in cells that are rapidly dividing but are avirulent in cells that are not dividing rapidly. Examiner never suggested that the constructs of Bolovan could be used in the method of the combined references.

Applicant's arguments drawn to MacLean et al, Amer et al,Budman et al appear to be factual but are not drawn to the combined teachings of the references.

As drawn to Olofsson et al, Applicant's argues that B16 mouse melanoma cells are in fact primary melanoma cells and therefore, the reference does not teach that HSV-1 infects metastatic melanoma cells and further, the teaching of Olofsson is limited to infection. The argument has been considered but has not been found persuasive, although Applicant specifically states that B16 cells are primary melanoma cells, this is clearly not the case. In addition, since these cells are known for their propensity to metastasize, cellular changes drawn to the invasive process and survival of the cancer cells in metastatic condition have clearly occurred. The cells therefore are certainly representative of metastatic melanoma cells. Further, as drawn to the limits to infection, Applicant is once again not drawing the response to the combined teachings of the references.

Applicant argues Martuza and Brown combined, reiterating arguments drawn to replication not being directly equated with the ability to lyse cells and the

inconsistency of Examiner's position in regard to Martuza looking for viruses which do not replicate in non-dividing cells. These arguments were considered above and were found to be not persuasive for the reasons set forth above.

Applicant argues that Olofsson, Bolovan, MacLean do not remedy the deficiencies of Brown and Martuza and reiterates arguments drawn to replication and virulence. The arguments have been considered but have not been found persuasive for the reasons set forth above.

Applicant argues that Examiner's statement that it would be expected that the 1716 construct would be virulent to intracranial rapidly dividing metastatic cells is mere speculation". The argument has been considered but has not been found persuasive because the statement is not mere speculation but based on the teachings of the prior art references for the reasons of record. It is suggested that Applicant review pages 6-7 of the Action of May 10, 2004.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

5. Claims 43-45, 47, 51, 59 remain rejected and claims 60-61 are rejected under 35 USC 103 for the reasons previously set forth in the paper mailed May 10, 2004, Section 4, pages 8-11.

Applicant states that Applicant is aware that the Examiner will consider the '673 patent enabled across the scope of the claims and then goes on to argue that the patent is not enabled. The arguments have been considered but have not been found persuasive because Applicant is correct, the Office considers the '673 patent enabled across the scope of the claims.

Applicant reiterates arguments drawn to replication and virulence. The arguments have been considered but have not been found persuasive for the reasons set forth above.

Applicant argues that the '673 patent does not discuss lysis but rather describes suppression of growth of the tumor and states that the process of tumor treatment of infection, replication and lysis does not occur, rather induction of apoptosis is proposed and Applicant points to col 5, lines 66-67 and/or column 25, lines 35-39.

The argument has been considered but has not been found persuasive because Applicant is misrepresenting the teachings of the '673 patent. A review of the cited teaches reveals the teaching that the attenuated 34.5 virus can induce apoptosis, but does not teach that the process of lysis does not occur. Again, Applicant is arguing references individually and does not take into account the teaching of the '845 patent.

Applicant reiterates arguments drawn to HSV1716. The arguments have been considered previously but have not been found persuasive for the reasons of record.

Applicant states that in the combination of Martuza and Roizman, any combination of these two references must involve a double mutation. The argument has been considered but has not been found persuasive because Examiner refers to the Martuza reference only for the motivation for using an HSV-1 mutant in the combined methods of Roizman and Brown for cancer therapy.

Applicant again calls into question the enablement of the Roizman patent. The argument was considered above but not found persuasive for the reasons set forth above.

Applicant argues that a hope of succeeding should not be confused with a reasonable expectation of success. The argument has been considered but has not been found persuasive because the reasons for a reasonable expectation of success were clearly delineated in the paper mailed May 10, 2004.

The arguments have been considered but has not been found persuasive and the rejection is maintained.

New Grounds of Objection

7. Claim 61 is objected to as a complete duplicate of claim 60. It appears that the submission of this claim was an inadvertent typographical error. Applicant is required to delete the duplicate claim or to amend the claim so that it does not duplicate claim 60.

8. No claims allowed.

9. All other objections and rejections recited in the paper mailed May 10, 2004 are hereby withdrawn.

10. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE

OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
January 4, 2005